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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/651,690	08/28/2003	Joanne Young Hee Kwak Kim	112461-016	9043

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/651,690	KIM ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-283* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,28-40,43-69,73-82,86-111,113-137,139-163,165-175,177-187 and 277-283* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 20-27,41,42,70-72,83-85,112,138,164,176 and 188-276.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 27, 2006 has been entered.

Note that applicant's petition to revive an unintentionally abandoned application was approved by Andrea Smith in the Office of Petitions on November 13, 2006.

Applicant's response and claim amendments received March 29, 2007 are acknowledged.

Claims 1-283 are pending.
Claims 1-4, 9, 11, 47, 48, 50, 51, 53, 55, 60, 63, 73, 75, 88, 93, 96, 115, 120, 123, 141, 146, 149, 167, 172, 179, and 185 have been amended.
Claims 20-27, 41, 42, 70-72, 83-85, 112, 138, 164, 176, and 188-276 stand withdrawn from consideration as being drawn to nonelected inventions. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the restriction requirement mailed August 25, 2004.

Claims 1-19, 28-40, 43-69, 73-82, 86-111, 113-137, 139-163, 165-175, 177-187 and 277-283 are under examination in the instant office action.

Declaration under 37 CFR 1.131

2. The declaration filed on May 26, 2006 under 37 CFR 1.131 has been considered but is ineffective to overcome the prior art reference of Pluenneke (of record).

The declaration is ineffective for many reasons. First, applicant has indicated in this declaration that the acts relied upon to antedate the prior art reference of Pluenneke was performed in the United States and this declaration has been signed by inventors Dr. Joanne Kwak-Kim and Dr. Alice Gilman-Sachs. The declaration also states that the third inventor, Alan E. Beer is deceased. As such, the declaration has been signed by only two of the three named inventors. Upon consultation with the Office of Legal Affairs, it was determined that a statement under 37 CFR 1.131 that a coinventor is dead is not sufficient to establish the death of the coinventor in the prosecution history. It was also suggested that since no rule exactly fits the instant fact pattern, applicant should file a petition under 37 CFR 1.183 to indicate that inventor Alan E. Beer is deceased. Therefore, the declaration is considered to have been signed by only some of the inventors of the instant application. As was stated in the office action mailed November 29, 2005, all inventors must sign a declaration under 37 CFR 1.131 to antedate a prior art reference.

Second, to be persuasive the declaration must provide evidence of conception of the instant invention that encompasses the full breadth of the invention as currently claimed. To this end, the declaration provides 2 exhibits. Exhibit 1 is a letter from Dr. Kwak-Kim indicating that *she* is preparing *her* idea for a possible clinical trial using etanercept. The letter does not indicate that others, such as inventors Beer and Gilman-Sachs, had any role in this idea. If this letter was to be found persuasive, it would immediately raise questions as to who invented the instant claimed methods. Further, applicants have claimed methods of treatment with various Th1 antagonists or Th2 agonists, not just treatment with the TNFα antagonist etanercept. Note that the claims recite numerous details and limitations that are not found in this letter. Exhibit 2 appears to comprise photocopied laboratory notebook pages that may concern the early steps in performing in vitro testing methods by ELISA and flow cytometry, although the handwriting and drawings present in the photocopied pages are hard to read and as such it is difficult to precisely ascertain what the pages disclose. None of the laboratory notebook pages appear to disclose any in vivo methods of treatment. As such, the evidence supplied to support the instant declaration does not demonstrate conception of

the treatment methods currently claimed in patentable detail. Specifically, all the steps concerning patient populations and subpopulations, diagnostic testing methodologies, and numerous administered agents appear to be lacking in the evidence of the declaration. As such, the evidence of the declaration does not support the invention as currently claimed.

Based on the above, the declaration filed on May 26, 2006 under 37 CFR 1.131 is not sufficient to antedate the prior art of Pluenneke.

Applicants have collectively argued that all rejections that include the teachings of Pluenneke should be withdrawn based upon the above discussed declaration. Since this declaration is not persuasive for the reasons stated above, none of the rejections of record have been withdrawn based upon this argument and this issue will not be further addressed in this office action.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. The rejection of claims 1-19, 28-40, 43-52 and 277 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, has been withdrawn in view of applicant's claim amendments received March 29, 2007.

Specifically, these amendments have addressed the issue of when immune response measurements take place.

5. Claims 1-4, 8-15, 28-40, 43-69, 73-82, and 151 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 1, 53, and 73 recite measuring an "in serum or intracellular Th1 (or Th2) immune response". What are the metes and bounds of this terminology?

The specification discloses that cytokines can be measured in serum and intracellularly, but cytokines appear only in dependent claims, such as claim 5. Further, dependent claims, such as claim 8, recite reducing absolute counts of Th1 cells. Cells are not present in serum, nor are they intracellular, but clearly a Th1 cell must be part of a Th1 immune response. As such, it is not clear what applicant is intending to claim by the recitation of measuring an "in serum or intracellular Th1 (or Th2) immune response".

Claim 151 depends from claim 124, which depends from independent claim 113. Claim 113 recites etanercept, not D2E7. As such, the recitation of D2E7 in claim151 lacks antecedent basis.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 8-15, 28-40, 43-69, 73-82, 88, 93, 96, 115, 120, 123, 141, 146, 149, 167, 172, 179, and 185 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant has amended claim 4 to recite "or percentage" and has not indicated where in the specification support for this amendment can be located. Upon review of the specification, while it appears that the specification discloses on page 7 that a Th1 to Th2 ratio can be created using absolute cell counts, the specification does not appear to indicate that such a ratio can be generated using a percentage of a population. As such, applicant's claim amendments appear to have introduced claim limitations not supported by the original disclosure.

Claims 3, 48, 51, 55, 60, 63, 75, 88, 93, 96, 115, 120, 123, 141, 146, 149, 167, 172, 179, and 185 have been amended to recite "wherein the ART includes all fertility treatments in which both eggs and sperm are handled". Again, applicant has not indicated where support for this limitation can be found. Lines 21-23 of page 1 of the specification disclose that ART includes in-vitro fertilization and other techniques, but it does not state that ART includes all techniques that require handling of eggs and sperm. As such, applicant's claim amendment appears to limit ART techniques to a particular subgenus of technologies that do not appear to be disclosed in the instant specification.

Independent claims 1, 53, and 73 recite measuring in serum or intracellular Th1 and Th2 responses. The specification discloses measuring the amount of Th1 cytokines IL-1, IL-2, TNFα and IFNγ present in patient serum or present in cells obtained from a patient as well as the measurement of Th2 cytokines IL-4, IL-5, IL-6, and IL-10 by the same methods (see particularly page 7). The specification does not appear to disclose the phrase "in serum or intracellular Th1 (or Th2) immune response", but this phrase must be broader in scope than cytokine responses since the phrase "in serum or intracellular Th1 (or Th2) immune response" is recited in independent claim 1 whereas measuring cytokine responses is a limitation recited in dependent claim 5 and properly dependent claims must be more narrow in scope than the claim the preceding claim. However, the specification does not appear to disclose what else in addition to cytokine levels are encompassed by the phrase "in serum or intracellular Th1 (or Th2) immune response". This broadening of the claimed invention in a manner not supported by the disclosure as originally filed appears to have introduced new matter into the claimed invention.

In response to this action, applicant should either point to where support for the instant claim limitations can be readily found, or remove the new limitations from the claimed invention.

8. Claims 1-19, 28-40, 43-69, and 73-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain

subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The disclosure of the instant specification is not sufficient to enable a skilled artisan to practice the claimed invention without conducting an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding in vivo methods which rely on previously undescribed and generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP also states that physiological activity can be considered inherently unpredictable.

Further, in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "[W]here there is "no indication that one skilled in [the] art would accept without question statements [as to the effects of the claimed drug products] and no evidence has been presented to demonstrate that the claimed products do have those effects," an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement" and "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions"

consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

Applicant has claimed broad methods in which Th1 antagonists or Th2 agonists are administered to a patient to treat infertility. The specification exemplifies cytokines that are considered to be either Th1 or Th2 cytokines, and provides examples of antagonists of specific cytokines, such as TNFα (see particularly pages 7-12). The claims are not limited to administering antagonists/agonists to alter cytokines but rather to alter immune responses. Immune responses are complex, involving both cell mediated and humoral responses.

Indeed, Th1/Th2 responses are generally considered in the context of T-helper cell activity, of which cytokine secretion is only a part of the response. It is known that splitting immune responses into these two pathways is an oversimplification, and it is well known that many other cell types, such as macrophages and dendritic cells can secret cytokines that influence immune responses (Kidd, see entire document, particularly the introduction and page 228). Further, distinct lineages of T cells, such as Th17 cells, have been discovered that appear to secrete a mixture of cytokines typically thought of as Th1 and Th2, such as TNFα and IL-6 (Harrington et al., see entire document particularly the top left column of page 351 and Figure 2). It is known that mixed patterns of cytokine secretion occur in many conditions, and that due to natural plasticity in vivo, the long term expression of only Th1 or Th2 type cytokines may be a property limited only to long-term T cell clones grown in vitro (Dent, see entire document, particularly page 268). As such, while it appears that in some patients with infertility a particular pattern of cytokine expression may predominate, this pattern does not necessarily apply to all Th1 and Th2 cytokines, since as explained above the

distinction between Th1 and Th2 is unclear as many cells can secrete both kinds of cytokines and because Th1/Th2 immune responses involve more than the simple elaboration of cytokines.

Additionally, while the prior art appears to disclose inhibitors of specific cytokines, such as TNFα, the prior art does not appear to disclose any antagonist that globally affects all Th1 responses, both cell-mediated and humoral, nor does it appear to disclose an antagonist that is limited to all Th1 cytokines, whatever they may be. The same can be said for Th2 agonists. Cytokines are quite diverse in their structure and the biological activities, with such activities often been cell type specific. Indeed, cytokines such as IFNγ are generally considered to be beneficial in expanding Th1 cells while inhibiting the expansion of other T cell subsets, such as Th17 (Harrington et al., see particularly Figure 3). Further, it is known that some of the biological effects of Th1 cells are mediated by cell to cell contact, such as the killing of Fas expressing cells due to expression of FasL on the Th1 cell (El-Khatib, see entire document). Given the diverse structures and activities involved in Th1 immune responses, it does not appear that any single agent could act as an antagonist of all Th1 responses, with the same being true for agonist of Th2 responses. Additionally, this complexity implies that measuring a ratio of only two cytokines, such as those recited in dependent claims, would not provide an accurate measurement of the overall ratio of Th1 immune activity to Th2 immune reactivity, especially given that such a measurement cannot account for cell-mediated activities.

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of working examples, the unpredictability of the art, and the breadth of the claims, a skilled artisan would be required to perform undue trials and errors to practice the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 86, 89-91, 94, 98-100, 103-111,113, 116-118, 121, 125, 126, 129-137, 139, 142-44, 147, 151-153, 155-163, 165, 168-170, 173, and 174 stand rejected under 35 U.S.C. 103(a), as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) for the reasons of record. The office action mailed November 29, 2005 states:

> Pluenneke discloses the use of agents that inhibit the activity or production of TNF-α in the treatment of many medical disorders (see entire document, particularly the abstract and paragraphs 8 and 9). Examples of TNF-α inhibiting agents that are useful in the methods disclosed by Pluenneke include the TNFR-Ig construct etanercept, as well as anti-TNF-α monoclonal antibodies including, but not limited to, infliximab, D2E7, and CDP571, as well as the TNF-α synthesis inhibitor pentoxyfilline (see particularly paragraphs 9, 19, 20, and 32). These reagents are to be used in treating disorders of the human female reproductive system and include multiple implant failure/infertility and spontaneous abortion (see particularly paragraph 73). It should be noted that methods that inhibit spontaneous abortion or infertility necessarily enhance the ability of a subject to carry an embryo to term. Suitable dosages and routes of administration for the reagents disclosed by Pluenneke are provided (see particularly paragraphs 26-32). Note the reagents can be administered once or multiple times (see particularly paragraph 29). The disclosed dosage ranges for etanercept and the anti-TNF-α monoclonal antibodies overlap with the ranges claimed by applicant, and these agents can be injected intravenously, intramuscularly, subcutaneously, or can be administered as aerosols, eyedrops, oral medications including pills, or topical forms such as lotions, gels, sprays or ointments (see particularly paragraph 26). Patient populations included for treatment using the methods and compositions of Pluenneke include both humans and non-human animals (see particularly paragraph 81).
>
> Animals have immune systems, and as such they will all have a population of Th1 and Th2 cells, and thus they necessarily comprise a Th1 to Th2 ratio. The teachings of Pluenneke provide methods and compositions to antagonize the Th1 cytokine TNF-α, and as such these methods necessarily alter the Th1 to Th2 ratio present in the subject being treated. These teachings differ from the claimed invention in that they do not teach the administration of the TNF-α antagonist prior to conception, or the administration of a TNF-α antagonist combined with lymphocyte immunization, intravenous IgG, anticoagulants or steroids such as prednisone.
>
> Coulam et al. teaches methods and clinical protocols for use in diagnosing and treating patients that suffer from recurrent spontaneous abortions (see entire document, particularly the introduction). These

methods include the administration of heparin, aspirin, prednisone, intravenous Ig, and immunization with paternal lymphocytes to treat such patients (see particularly Table IV). The methods of Coulam et al. only specify IVIg and not a specific Ig isotype, but the most abundant isotype in blood plasma is IgG, and as such Coulam et al. teach the administration of IgG to patients (see particularly the paragraph that spans pages 3.2 and 3.3 of Janeway et al. and the paragraph that spans pages 67 to 68 of Coulam et al.). Table IV of Coulam et al. indicates that many of the therapeutic interventions may or must be initiated before conception, such therapies including the use of aspirin, prednisone, and therapeutic immunization with lymphocytes (see particularly the first full paragraph of page 67 and Table IV). All of these treatments initiated prior to conception are intended to increase the odds that a successful conception and delivery to term will result (see particularly from the middle of the right column of page 66 to the end of the left column of page 67). Indeed, Coulam et al. specifically state that initiating immunotherapy preconceptually as compared with postconceptually offers the advantage of significantly increase live birth rates (see particularly the first full sentence of the left column of page 68).

Both Pluenneke and Coulam et al. teach methods and composition that treat spontaneous abortion and infertility. As such, "It is *prima facie* obvious to combine two compositions (or methods) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

It would also have been *prima facie* obvious to a person of ordinary skill in the art to administer just the TNF-α antagonists of Pluenneke prior to conception. A person of ordinary skill in the art would have been motivated to administer just the TNF-α antagonist at this time based upon the teachings of Coulam et al. that many therapeutic interventions are initiated prior to conception in order to increase the odds of achieving a successful conception and pregnancy, and that doing so significantly increases live birth rates. Therefore, initiating treatment with a TNF-α antagonist prior to conception would gain the advantage of increasing the probability that the therapeutic intervention would be successful in inhibiting spontaneous abortion or implantation failure as evidenced by an increased live birth rate.

The rejection is maintained.

11. The rejection of claims 53, 56, 61, and 73 under 35 U.S.C. 103(a) as being unpatentable over Chaouat et al. (J. Immunol., 1995, 154:4261-4268, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) has been withdrawn in view of applicant's claim amendments received March 29, 2007.

Specifically, applicant has amended independent claims 53 and 73 to indicate that blood samples are withdrawn and tested for the presence of cytokines prior and subsequent to the administration of an antagonist of TNF-α.

12. The rejection of claims 53, 56, 61, and 73 under 35 U.S.C. 103(a) as being unpatentable over Chaouat (Cell Immunol., 1994, 157:328-340, see entire document) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire

document, of record) has been withdrawn in view of applicant's claim amendments received March 29, 2007.

Specifically, applicant has amended independent claims 53 and 73 to indicate that blood samples are withdrawn and tested for the presence of cytokines prior and subsequent to the administration of an antagonist of TNF-α.

13. Claims 177, 180-183, and 186 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) as applied to claims 86, 89-91, 94, 98-100, 103-111,113, 116-118, 121, 125, 126, 129-137, 139, 142-44, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) for the reasons of record.

The office action mailed November 29, 2005 states:

> The teachings of Pluenneke, Coulam et al. and Janeway et al. have been discussed above. These teachings differ from the claimed invention in that Pluenneke does not disclose the anti-TNFα monoclonal antibody CDP870 as part of his non-limiting examples of anti-TNFα antibodies that are suitable for use in methods of treating infertility and spontaneous abortion.
>
> Athwal et al. disclose the creation of the anti-TNFα antibody CDP870 (see entire document, particularly Figure 22 and paragraphs 231-266). This antibody is capable of neutralizing TNF-α and is comparable in efficacy to etanercept (see particularly paragraph 262). CDP870 is disclosed as being PEGylated, and as such it has a long plasma half life that is desirable for the treatment of patients (see particularly paragraphs 67 and 26).
>
> Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Athwal et al. for the anti-TNFα reagents, such as etanercept, used in the methods of Pluenneke with modified timing of administration as taught by Coulam et al. Motivation to make this substitution comes from the teachings of Athwal et al. that increased plasma half life of a reagent is desirable for treating patients and that CDP870 is PEGylated to increase its plasma half life. Therefore, a person of ordinary skill in the art would have been motivated to use CDP870 in the methods of Pluenneke et al. as modified by Coulam et al. since CDP870 has a comparable efficacy to etanercept, and since CDP870 has the advantage of being PEGlylated to increase its half life, thus making CDP870 an ideal reagent for treating patients as taught by Athwal et al.

The rejection is maintained.

14. Claims 101, 102, 127, 128, 154, 175, and 280-282 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997,

38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) as applied to claims 86, 89-91, 94, 98-100, 103-111,113, 116-118, 121, 125, 126, 129-137, 139, 142-44, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of in view of Terao et al. (US Patent No. 6,013,252, see entire document, of record) for the reasons of record.

The office action mailed November 29, 2005 states:

> The teachings of Pluenneke, Coulam et al. and Janeway et al. have been discussed above. These teachings differ from the claimed invention in that while they do teach TNF-α antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.
>
> Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the final paragraph of column 8 and Example 3. Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).
>
> Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors that are used in methods of inhibiting spontaneous abortion or infertility, (which are also methods that promote conception and the maintenance of pregnancy) as taught by Pluenneke and modified by the teachings of Coulam et al. and Janeway et al., into a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al. that gels or other form that can be applied vaginally offer the advantage of being easily administered to the patient.

The rejection is maintained.

15. Claims 187 and 283 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) and in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) as applied to claims 86, 89-91, 94, 98-100, 103-111,113, 116-118, 121, 125, 126, 129-137, 139, 142-44, 147, 151-153, 155-163, 165, 168-170, 173, 174, 177, 180-183, and 186 above, and further in view of in view of Terao et al. (US Patent No. 6,013,252, see entire document, of record) for the reasons of record.

The office action mailed November 29, 2005 states:

> The teachings of Pluenneke, Coulam et al., Janeway et al. and Athwal et al. have been discussed above. These teachings differ from the claimed invention as recited in claims 187 and 283 in that while they do teach TNF-α antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.
>
> Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the

final paragraph of column 8 and Example 3. Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors of Pluenneke and Athwal et al. that are used in methods of inhibiting spontaneous abortion or infertility, (which are also methods that promote conception and the maintenance of pregnancy) with the timing of administration modified by the teachings of Coulam et al., into a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al. that gels or other form that can be applied vaginally offer the advantage of being easily administered to the patient.

The rejection is maintained.

16. The rejection of claims 1, 5, 6, 12-19, 28-39, 43-46, and 49 under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) as applied to claims 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) has been withdrawn in view of applicant's claim amendments received March 29, 2007.

Specifically, the independent claims have been amended to recite that blood samples are withdrawn and tested for the presence of cytokines prior and subsequent to the administration of a therapeutic agent, such as an antagonist of TNF-α.

17. The rejection of claims 40, 69, 82, and 177, 180-183, and 186 under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) and in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) as applied to claims 1, 5, 6, 12-19, 28-39, 43-46, and 49, 53, 56-58, 61, 65-68, 73, 76-81, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174

above, and further in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) has been withdrawn in view of applicant's claim amendments received March 29, 2007.

Specifically, the independent claims have been amended to recite that blood samples are withdrawn and tested for the presence of cytokines prior and subsequent to the administration of a therapeutic agent, such as the anti-TNF-α antibody CDP870.

18. The rejection of claim 277 under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) and in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) as applied to claims 1, 5, 6, 12, 14, 16-19, 28-31, 33-39, 43-46, 49, 53, 56-58, 61, 65-68, 73, 76-81, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of Terao et al. (US Patent No. 6,013,252, see entire document, of record) has been withdrawn in view of applicant's claim amendments received March 29, 2007.

Specifically, the independent claims have been amended to recite that blood samples are withdrawn and tested for the presence of cytokines prior and subsequent to the administration of a therapeutic agent, such as an antagonist of TNF-α.

19. Claims 1, 5, 6, 12-19, 28-39, 43-46, 49, 53, 56-58, 61, 65-68, 73, and 76-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) as applied to claims 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and

further in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) and further in view of Le et al. (US patent 5,656,272, see entire document).

The teachings of Pluenneke, Coulam et al. and Janeway et al. have been discussed above. In summary, these teachings indicate that all women suffering from disorders of the female reproductive system such as multiple implant failure/infertility and spontaneous abortion should be treated with TNF-α antagonists, and that treatment is most effective when it begins prior to conception. These teachings differ from the claimed invention in that they do not disclose the measurement of the Th1 to Th2 ratio in patients being treated for spontaneous abortions or infertility prior and subsequent to treatment with a therapeutic agent.

Raghupathy et al. teach that significantly greater levels of the Th2 cytokines IL-6 and IL-10 were found in normal pregnancy as compared to women with a history of unexplained recurrent spontaneous abortions (RSA), and that significantly higher levels of the Th1 cytokine IFN-γ were found in RSA as compared to normal pregnancy (see entire document, particularly the abstract). Raghupathy et al. calculated the ratio of Th2 to Th1 cytokines because the ratio of these cytokines is more important than their mere presence or absence (see particularly the left column of page 125, the first full paragraph of the left column of page 127, and Table 1). Their data demonstrates a distinctly increased Th2 bias in normal pregnancy and an increased Th1 bias in RSA (see particularly the first full paragraph of the left column of page 127). The cytokines measured by Raghupathy et al. include the Th2 cytokines IL-4, IL-5, IL-6, IL-10, and the Th1 cytokines IL-2, IFN-γ, TNF-β and TNF-α (see particularly the section titled Cytokine profiles in MLPR on page 124). One particular ratio calculated by Raghupathy et al. was IL-10:TNF-α, although ratios comparing any of the cytokines measured by Raghupathy would have been obvious to calculate (see particularly Table 1). These cytokines are disclosed as having been measured from PBMC stimulated *in vitro* with either irradiated placental cells (MLPR) or soluble antigen (see particularly the materials and methods section) or alternatively, the cytokines were measured directly from patient

sera (see particularly the first full paragraph of page 129). Serum cytokine measurements indicated significantly increased IL-6 and IL-10 levels in normal pregnancy as compared to RSA, with significantly increased TNF-α detected in serum from recurrent aborters (see particularly the first full paragraph of page 129).

Raghupathy et al. further teach that appropriate interventions that shift the ratio of immune reactivity toward Th2 dominance or that inhibit Th1 cytokine production are to be administered to patients to help them achieve a successful pregnancy, and that not all women suffering from RSA demonstrate an immunological etiology such as an increased level of Th1 cytokines (see particularly the last two paragraphs of page 129). As such, the identification of patients that have altered cytokine ratios would allow for the more efficacious targeting of immunological therapeutic interventions to only the subset of patients who are likely to be responsive to such interventions (see particularly the last two paragraphs of page 129).

Le et al. teach that measuring cytokines obtained from patients before and after treatment with anti-TNF-α antibodies is one way to determine the clinically efficacy of treating a disease or condition by administering anti-TNF-α antibodies (see entire document, particularly Example XXII, Table 9A and the paragraph spanning columns 77 and 78).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure the Th1 to Th2 ratio of patients as taught by Raghupathy et al. before performing the therapeutic methods of Pluenneke as modified by Coulam et al. Motivation to incorporate this method step comes from the teachings of Raghupathy et al. that not all cases of spontaneous abortion have an immunological etiology, but in those cases that do, therapeutic methods designed to alter the Th1 to Th2 ratio are useful in helping such women achieve a successful pregnancy. As such, incorporation of a screening method to identify women that suffer spontaneous abortion of immunological etiology into the treatment methods collectively taught by Pluenneke as modified by Coulam et al. would offer the advantage of targeting immunotherapy to only those patients that are likely to benefit from such

interventions. A person of ordinary skill in the art would have also been motivated to repeat the measurement of the Th1 to Th2 ration to determine if the administered agent was having the expected therapeutic effect as was taught by Le et al. As such, repeated determinations of the Th1 to Th2 ratio allows for the initial selection of patients likely to benefit from treatment and provides an indication as to the efficacy of the selected treatment method.

20. Claims 40, 69, and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) and in view of Le et al. (US patent 5,656,272, see entire document) as applied to claims 1, 5, 6, 12-19, 28-39, 43-46, 49, 53, 56-58, 61, 65-68, 73, 76-81, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record).

The teachings of Pluenneke, Coulam et al., Janeway et al., Raghupathy et al. and Le et al. have been discussed above. These teachings differ from the claimed invention in that they do not disclose the use of the anti-TNF-α antibody CDP870.

Athwal et al. disclose the creation of the anti-TNFα antibody CDP870 (see entire document, particularly Figure 22 and paragraphs 231-266). This antibody is capable of neutralizing TNF-α and is comparable in efficacy to etanercept (see particularly paragraph 262). CDP870 is disclosed as being PEGylated, and as such it has a long plasma half life that is desirable for the treatment of patients (see particularly paragraphs 67 and 26).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Athwal et al. for the anti-TNFα

reagents, such as etanercept, used in the methods of collectively taught by Pluenneke, Coulam et al., Janeway et al., Raghupathy et al. and Le et al. Motivation to make this substitution comes from the teachings of Athwal et al. that increased plasma half life of a reagent is desirable for treating patients and that CDP870 is PEGylated to increase its plasma half life. Therefore, a person of ordinary skill in the art would have been motivated to use CDP870 in place of other TNF-α antagonists because CDP870 has a comparable efficacy to etanercept, and since CDP870 has the advantage of being PEGlylated to increase its half life, thus making CDP870 an ideal reagent for treating patients as taught by Athwal et al.

21. Claims 2-4, 7-11, 47, 48, 50-52, 54, 55, 59, 60, 62-64, 74, 75, 87, 88, 92, 93, 95-97, 114, 115, 119, 120, 122-124, 140, 141, 145, 146, 148-150, 166, 167, 171, 172, 178, 179, 184, and 185 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) in view of Le et al. (US patent 5,656,272, see entire document) and in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) as applied to claims 1, 5, 6, 12-19, 28-40, 43-46, 49, 53, 56-58, 61, 65-69, 73, 76-82, 86, 89-91, 94, 98-100, 103-111, 113, 116-118, 121, 125, 126, 129-137, 139, 142-144, 147, 151-153, 155-163, 165, 168-170, 173, and 174 above, and further in view of Ng et al. (Am. J. Reproductive Immunol., 2002, 48:77-86, Presented at the ASRI XXIst Annual Meeting in Chicago, June 9-12 2001, of record on PTO form 1449 filed May 19, 2004) as evidenced by Alak et al. (US patent No. 5,693,534, see entire document) for the reasons of record.

The teachings of Pluenneke, Coulam et al., Janeway et al., Raghupathy et al., Le et al. and Athwal et al. have been discussed above. These teachings differ from the instant claimed invention in that they do not disclose measuring the Th1 to Th2 cytokine ratio using absolute cell counts or by intracellular cytokine staining. These teachings

also do not explicitly indicate the treatment of the patients that have undergone the specific assisted reproductive technologies of *in vitro* fertilization or ovulation induction cycles.

Ng et al. teach that there are changes in both absolute counts of T cells that express Th1 and Th2 cytokines, as well as changes in the ratio of these cytokines, when comparing women diagnosed with recurrent spontaneous abortions or who had multiple implantation failures after *in vitro* fertilization and embryo transfer (IVF/ET) with normal pregnancy controls (see entire document, particularly the abstract). Ovulation induction is a routine part of IVF therapy that increases the number of eggs that are retrieved and available for use in IVF therapy, and as such women that have undergone IVF have also undergone ovulation induction therapy (see Alak et al., particularly column 5, lines 16-34). The data obtained by Ng et al. was collected by intracellular cytokine staining of PBMC isolated from study participants (see particularly the Materials and Methods section). Ng et al. demonstrated that the absolute T cell counts of TNF-α expressing CD3+/CD4+ T cells were significantly increased in implantation failure patients as compared to normal controls (see particularly the paragraph that spans pages 80 and 81). Ng et al. also disclose that increased Th1/Th2 cytokine ratios were observed in women with recurrent pregnancy losses and multiple implantation failures after IVF/ET as compared with normal controls (see particularly the paragraph that spans the right and left columns of page 78). Cytokine ratios compared by Ng et al. include INF-γ/IL-4, INF-γ/IL-10, TNF-α/IL-4, TNF-α/IL10 (see particularly the final paragraph of the results section on page 82). Of these the ratio of TNF-α to IL-10 appeared most important since patients with implantation failures after IVF/ET had an up-regulated TNF-α level and a down-regulated IL-10 level as compared to controls (see particularly Table III, the first paragraph of the discussion on page 82, the paragraph that spans pages 83-84, and the penultimate paragraph on page 84).

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to substitute the cytokine detection methods and patient populations taught by Ng et al. for the methods taught collectively by the

teachings of Pluenneke, Coulam et al., Janeway et al., Raghupathy et al., Le et al. and Athwal et al. Motivation to make these substitutions comes from Raghupathy et al.'s teachings that it is important to identify women suffering from spontaneous abortion that would benefit from immunological interventions that alter a woman's Th1 to Th2 ratio, and Ng et al.'s teaching of methods that use intracellular cytokine staining and absolute cell counts to identify additional women, such as those undergoing IVF/ET, that would benefit from interventions that alter the Th1 to Th2 ratio. A person of ordinary skill in the art would also have been motivated at the time the invention was made to reduce the absolute counts of CD3+/CD4+ T cells that express TNF-α since this population was shown by Ng et al. to be increased in patients that suffer spontaneous abortions and implantation failure, and the teachings of Pluenneke that methods that suppress the expression of TNF-α are to be used in treating conditions mediated by increased levels of TNF-α, such conditions including multiple implant failure/infertility and spontaneous abortion.

22. Claims 101, 102, 127, 128, 154, 175, and 277-283 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document, of record) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document, of record) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3, of record) in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document) in view of Le et al. (US patent 5,656,272, see entire document) and in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record) in view of Ng et al. (Am. J. Reproductive Immunol., 2002, 48:77-86, Presented at the ASRI XXIst Annual Meeting in Chicago, June 9-12 2001, of record on PTO form 1449 filed May 19, 2004) as evidenced by Alak et al. (US patent No. 5,693,534, see entire document) as applied to claims 1-19, 28-40, 43-69, 73-82, 86-100, 103-111, 113-126, 129-137, 139-153, 155-163, 165-174 above, and further in view of Terao et al. (US Patent No. 6,013,252, of record)

The collective teachings of Pluenneke, Coulam et al., Raghupathy et al., Le et al., Athwal et al., and Ng et al. have been discussed above. These teachings differ from the claimed invention in that while they do teach TNF-α antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.

Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the final paragraph of column 8 and Example 3. Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors in a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al. that gels or other forms that can be applied vaginally offer the advantage of being easily administered to the patient.

23. Claims 113, 116-118, 121, 125-126, and 129-137 are rejected under 35 U.S.C. 103(a), as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record).

Finck discloses the use of agents that inhibit the activity or production of TNF-α in the treatment of many medical disorders (see entire document, particularly the abstract and page 1). Examples of TNF-α inhibiting agents that are useful in the methods disclosed by Finck include the TNFR-Ig construct etanercept, as well as anti-TNF-α monoclonal antibodies and the TNF-α synthesis inhibitor pentoxyfilline (see particularly pages 4 and 5). These reagents are to be used in treating disorders of the human female reproductive system and include multiple implant failure/infertility and spontaneous abortion (see particularly page 15). It should be noted that methods that inhibit spontaneous abortion or infertility necessarily enhance the ability of a subject to carry an embryo to term. Suitable dosages, routes, and frequency of administration for

the reagents disclosed by Finck are provided (see particularly page 8). Note that the reagents of Finck can be administered once or multiple times (ibid). TNF-α inhibitors are disclosed as being administered by many routes, including intravenously, intramuscularly, subcutaneously, or as aerosols, eyedrops, oral medications including pills, or topical forms such as lotions, gels, sprays or ointments (see particularly page 7). Patient populations included for treatment using the methods and compositions of Pluenneke include both humans and non-human animals (see particularly paragraph 81).

Animals have immune systems, and as such they will all have a population of Th1 and Th2 cells, and thus they comprise a Th1 to Th2 ratio. The teachings of Finck provide methods and compositions to antagonize the Th1 cytokine TNF-α, and as such these methods alter the Th1 to Th2 ratio present in the subject being treated. These teachings differ from the claimed invention in that they do not teach the administration of the TNF-α antagonist prior to conception, or the administration of a TNF-α antagonist combined with lymphocyte immunization, intravenous IgG, anticoagulants or steroids such as prednisone.

Coulam et al. teaches methods and clinical protocols for use in diagnosing and treating patients that suffer from recurrent spontaneous abortions (see entire document, particularly the introduction). These methods include the administration of heparin, aspirin, prednisone, intravenous Ig, and immunization with paternal lymphocytes to treat such patients (see particularly Table IV). The methods of Coulam et al. specify IVIg, but given that the most abundant isotype in blood plasma is IgG, Coulam et al. teach the administration of IgG to patients (see particularly the paragraph that spans pages 3.2 and 3.3 of Janeway et al. and the paragraph that spans pages 67 to 68 of Coulam et al.). Table IV of Coulam et al. indicates that many of the therapeutic interventions may or must be initiated before conception, such therapies including the use of aspirin, prednisone, and therapeutic immunization with lymphocytes (see particularly the first full paragraph of page 67 and Table IV). All of these treatments initiated prior to conception are intended to increase the odds that a successful conception and delivery to term will

result (see particularly from the middle of the right column of page 66 to the end of the left column of page 67). Indeed, Coulam et al. specifically state that initiating immunotherapy preconceptually as compared with postconceptually offers the advantage of significantly increasing live birth rates (see particularly the first full sentence of the left column of page 68).

Both Finck and Coulam et al. teach methods and composition that treat spontaneous abortion and infertility. As such, "It is *prima facie* obvious to combine two compositions (or methods) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

It would also have been *prima facie* obvious to a person of ordinary skill in the art to administer the TNF-α antagonists of Pluenneke prior to conception. A person of ordinary skill in the art would have been motivated to administer just the TNF-α antagonist at this time based upon the teachings of Coulam et al. that many therapeutic interventions are initiated prior to conception in order to increase the odds of achieving a successful conception and pregnancy, and that doing so significantly increases live birth rates. Therefore, initiating treatment with a TNF-α antagonist prior to conception would gain the advantage of increasing the probability that the therapeutic intervention would be successful in inhibiting spontaneous abortion or implantation failure as evidenced by an increased live birth rate.

24. Claims 127 and 128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) as applied to claims 113, 116-118, 121, 125-126, and 129-137 above, and further in view of in view of Terao et al. (of record)

The teachings of Finck and Coulam et al. have been discussed above. These teachings differ from the claimed invention in that while they do teach TNF-α

antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.

Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the final paragraph of column 8 and Example 3. Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors that are used in methods of inhibiting spontaneous abortion or infertility, (which are also methods that promote conception and the maintenance of pregnancy) as taught by Finck and Coulam et al. into a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al. that gels or other form that can be applied vaginally offer the advantage of being easily administered to the patient

25. Claims 1, 5, 6, 12-19, 28-37, 43-46, 49, 53, 56-58, 61, 65, 66, 73, 76-79, 86, 89-91, 94, 98-111, and 277-280 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) and in view of Terao et al. (of record) as applied to claims 113, 116-118, 121, and 125-137 above, and further in view of Raghupathy et al. (of record) and in view of Le et al (US patent 5,656,272).

The teachings of Finck, Coulam et al., and Terao et al. have been discussed above. In summary, these teachings indicate that all women suffering from disorders of the female reproductive system such as multiple implant failure/infertility and spontaneous abortion should be treated with TNF-α antagonists, and that treatment is most effective when it begins prior to conception. These teachings differ from the claimed invention in that they do not teach the measurement of a Th1 to Th2 ratio prior and subsequent to initiating treatment with a TNF-α inhibitor.

Raghupathy et al. teach that significantly greater levels of the Th2 cytokines IL-6 and IL-10 were found in normal pregnancy as compared to women with a history of unexplained recurrent spontaneous abortions (RSA), and that significantly higher levels of the Th1 cytokine IFN-γ were found in RSA as compared to normal pregnancy (see entire document, particularly the abstract). Raghupathy et al. calculated the ratio of Th2 to Th1 cytokines because the ratio of these cytokines is more important than their mere presence or absence (see particularly the left column of page 125, the first full paragraph of the left column of page 127, and Table 1). Their data demonstrates a distinctly increased Th2 bias in normal pregnancy and an increased Th1 bias in RSA (see particularly the first full paragraph of the left column of page 127). The cytokines measured by Raghupathy et al. include the Th2 cytokines IL-4, IL-5, IL-6, IL-10, and the Th1 cytokines IL-2, IFN-γ, TNF-β and TNF-α (see particularly the section titled Cytokine profiles in MLPR on page 124). One particular ratio calculated by Raghupathy et al. was IL-10:TNF-α, although ratios comparing any of the cytokines measured by Raghupathy would have been obvious to calculate (see particularly Table 1). These cytokines are disclosed as having been measured from PBMC stimulated *in vitro* with either irradiated placental cells (MLPR) or soluble antigen (see particularly the materials and methods section) or alternatively, the cytokines were measured directly from patient sera (see particularly the first full paragraph of page 129). Serum cytokine measurements indicated significantly increased IL-6 and IL-10 levels in normal pregnancy as compared to RSA, with significantly increased TNF-α detected in serum from recurrent aborters (see particularly the first full paragraph of page 129).

Raghupathy et al. further teach that appropriate interventions that shift the ratio of immune reactivity toward Th2 dominance or that inhibit Th1 cytokine production are to be administered to patients to help them achieve a successful pregnancy, and that not all women suffering from RSA demonstrate an immunological etiology such as an increased level of Th1 cytokines (see particularly the last two paragraphs of page 129). As such, the identification of patients that have altered cytokine ratios would allow for the more efficacious targeting of immunological therapeutic interventions to only the

subset of patients who are likely to be responsive to such interventions (see particularly the last two paragraphs of page 129).

Le et al. teach that measuring cytokines obtained from patients before and after treatment with anti-TNF-α antibodies is one way to determine the clinically efficacy of treating a disease or condition by administering anti-TNF-α antibodies (see entire document, particularly Example XXII, Table 9A and the paragraph spanning columns 77 and 78). One specific anti-TNF-α antibody disclosed by Le et al. is cA2, also known as infliximab/Remicade®, which has the advantageous properties of not crossreacting with related antigens, such as TNF-β, and safe, successful in vivo human use (see particularly the middle of column 20 and Examples XVI-XXIII).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure the Th1 to Th2 ratio of patients as taught by Raghupathy et al. before performing initiating therapy with a TNF-α inhibitor. Motivation to do so comes from the teachings of Raghupathy et al. that not all cases of spontaneous abortion have an immunological etiology, but in those cases that do, therapeutic methods designed to alter the Th1 to Th2 ratio are useful in helping such women achieve a successful pregnancy. As such, incorporation of a screening method to identify women that suffer spontaneous abortion of immunological etiology into the treatment method would offer the advantage of targeting immunotherapy to only those patients that are likely to benefit from such interventions. A person of ordinary skill in the art would have also been motivated to repeat the measurement of the Th1 to Th2 ratio to determine if the administered agent was having the expected therapeutic effect as was taught by Le et al. As such, repeated determinations of the Th1 to Th2 ratio allows for the initial selection of patients likely to benefit from treatment and provides an indication as to the efficacy of the selected treatment method. Further, it would have been obvious to a person of ordinary skill in the art to use the anti-TNF-α antibody of Le et al. in methods of treating infertility because Le et al. disclose that there antibody does not crossreact with other cytokines such as TNF-β and that it can be safely and successfully used in vivo in humans.

26. Claims 2-4, 7-11, 47, 48, 50-52, 54, 55, 59, 60, 62-64, 74, 75, 87, 88, 92, 93, 95-97, 114, 115, 119, 120, and 122-124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) in view of Terao et al. (of record) in view of Raghupathy et al. (of record) and in view of Le et al. (US patent 5,656,272) as applied to claims 1, 5, 6, 12-19, 28-37, 43-46, 49, 53, 56-58, 61, 65, 66, 73, 76-79, 86, 89-91, 94, 98-111, 113, 116-118, 121, 125-137 and 277-280 above, and further in view of Ng et al. (of record) as evidenced by Alak et al. (of record).

The teachings of Pluenneke, Coulam et al., Raghupathy et al., and Le et al. have been discussed above. These teachings differ from the instant claimed invention in that they do not disclose measuring the Th1 to Th2 cytokine ratio using absolute cell counts or by intracellular cytokine staining. These teachings also do not explicitly indicate the treatment of the patients that have undergone the specific assisted reproductive technologies of *in vitro* fertilization or ovulation induction cycles.

Ng et al. teach that there are changes in both absolute counts of T cells that express Th1 and Th2 cytokines, as well as changes in the ratio of these cytokines, when comparing women diagnosed with recurrent spontaneous abortions or who had multiple implantation failures after *in vitro* fertilization and embryo transfer (IVF/ET) with normal pregnancy controls (see entire document, particularly the abstract). Ovulation induction is a routine part of IVF therapy that increases the number of eggs that are retrieved and available for use in IVF therapy, and as such women that have undergone IVF have also undergone ovulation induction therapy (see Alak et al., particularly column 5, lines 16-34). The data obtained by Ng et al. was collected by intracellular cytokine staining of PBMC isolated from study participants (see particularly the Materials and Methods section). Ng et al. demonstrated that the absolute T cell counts of TNF-α expressing CD3+/CD4+ T cells were significantly increased in implantation failure patients as compared to normal controls (see particularly the paragraph that spans pages 80 and 81). Ng et al. also disclose that increased Th1/Th2 cytokine ratios were observed in women with recurrent pregnancy losses and multiple implantation

failures after IVF/ET as compared with normal controls (see particularly the paragraph that spans the right and left columns of page 78). Cytokine ratios compared by Ng et al. include INF-γ/IL-4, INF-γ/IL-10, TNF-α/IL-4, TNF-α/IL10 (see particularly the final paragraph of the results section on page 82). Of these the ratio of TNF-α to IL-10 appeared most important since patients with implantation failures after IVF/ET had an up-regulated TNF-α level and a down-regulated IL-10 level as compared to controls (see particularly Table III, the first paragraph of the discussion on page 82, the paragraph that spans pages 83-84, and the penultimate paragraph on page 84).

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to use the cytokine detection methods and patient populations taught by Ng et al. in the methods collectively taught by Pluenneke, Coulam et al., Raghupathy et al., and Le et al. Motivation to do so comes from Raghupathy et al.'s teachings that it is important to identify women suffering from spontaneous abortion that would benefit from immunological interventions that alter a woman's Th1 to Th2 ratio, and Ng et al.'s teaching of methods that use intracellular cytokine staining and absolute cell counts to identify additional women, such as those undergoing IVF/ET, that would benefit from interventions that alter the Th1 to Th2 ratio. A person of ordinary skill in the art would also have been motivated at the time the invention was made to reduce the absolute counts of CD3+/CD4+ T cells that express TNF-α since this population was shown by Ng et al. to be increased in patients that suffer spontaneous abortions and implantation failure, and the teachings of Finck that methods that suppress the expression of TNF-α are to be used in treating conditions mediated by increased levels of TNF-α, such conditions including multiple implant failure/infertility and spontaneous abortion.

27. Claims 40, 69, and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) in view of Terao et al (of record) in view of Raghupathy et al. (of record) in view of Le et al. (US patent 5,656,272) and in view of

Ng et al. (of record) as evidenced by Alak et al. (of record) as applied to claims 1-19, 28-37, 43-66, 73-79, 86-111, 113-137, and 277-280 above, and further in view of Athwal et al. (US 2002/0151682 A1, see entire document, of record).

The teachings of Finck, Coulam et al., Raghupathy et al. Le et al., and Ng et al. have been discussed above. These teachings differ from the claimed invention in that they do not disclose the use of the anti-TNF-α antibody CDP870.

Athwal et al. disclose the creation of the anti-TNFα antibody CDP870 (see entire document, particularly Figure 22 and paragraphs 231-266). This antibody is capable of neutralizing TNF-α and is comparable in efficacy to etanercept (see particularly paragraph 262). CDP870 is disclosed as being PEGylated, and as such it has a long plasma half life that is desirable for the treatment of patients (see particularly paragraphs 67 and 26).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Athwal et al. for the anti-TNFα reagents, such as etanercept, used in the methods of collectively taught by Pluenneke, Coulam et al., Janeway et al., Raghupathy et al., Le et al., and Ng et al. Motivation to make this substitution comes from the teachings of Athwal et al. that increased plasma half life of a reagent is desirable for treating patients and that CDP870 is PEGylated to increase its plasma half life. Therefore, a person of ordinary skill in the art would have been motivated to use CDP870 in place of other TNF-α antagonists because CDP870 has a comparable efficacy to etanercept, and since CDP870 has the advantage of being PEGlylated to increase its half life, thus making CDP870 an ideal reagent for treating patients as taught by Athwal et al.

28. Claims 38, 67, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) in view of Terao et al (of record) in view of Raghupathy et al. (of record) in view of Le et al. (US patent 5,656,272) and in view of Ng et al. (of record) as evidenced by Alak et al. (of record) as applied to claims 1-19,

28-37, 43-66, 73-79, 86-111, 113-137, and 277-280above, and further in view of Salfeld et al. (US patent 6,090,382).

The teachings of Finck, Coulam et al., Raghupathy et al. Le et al., and Ng et al. have been discussed above. These teachings differ from the claimed invention in that they do not disclose the use of the anti-TNF-α antibody D2E7.

Salfeld et al. disclose the creation of the anti-TNFα antibody D2E7, also known as adalimumab or Humira™ (see entire document, particularly the abstract, Figures 7 and 8, and the bottom of column 2). This antibody is capable of neutralizing TNF-α, does not crossreact with other cytokines and is a human antibody (see particularly columns 9 and 10). Since the antibody is human, it offers the advantage of being less immunogenic and thus is not subject to neutralization by a HAMA response in the therapeutically treated patient (see particularly column 2).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Salfeld et al. for the anti-TNFα reagents, such as etanercept, used in the methods of collectively taught by Pluenneke, Coulam et al., Janeway et al., Raghupathy et al., Le et al., and Ng et al. Motivation to make this substitution comes from the teachings of Salfeld et al. that their antibody is fully human and thus safer for use in humans since their antibody will not elicit a HAMA response.

29. Claims 39, 68, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finck (WO 00/62790) in view of Coulam et al. (of record) as evidenced by Janeway et al. (of record) in view of Terao et al (of record) in view of Raghupathy et al. (of record) in view of Le et al. (US patent 5,656,272) and in view of Ng et al. (of record) as evidenced by Alak et al. (of record) as applied to claims 1-19, 28-37, 43-66, 73-79, 86-111, 113-137, and 277-280above, and further in view of Adair et al. (US Patent 5,994,510, see entire document).

The teachings of Finck, Coulam et al., Raghupathy et al. Le et al., and Ng et al. have been discussed above. These teachings differ from the claimed invention in that they do not disclose the use of the anti-TNF-α antibody CDP571.

Adair et al. disclose the creation of the anti-TNFα antibody CDP571 (see entire document, particularly the abstract and Examples 2-4). This antibody is capable of neutralizing TNF-α and has been successfully used in vivo methods of treatment (see particularly Example 4).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Adair et al. for the anti-TNFα reagents, such as etanercept, used in the methods of collectively taught by Pluenneke, Coulam et al., Janeway et al., Raghupathy et al., Le et al., and Ng et al. Motivation to make this substitution comes from the teachings of Adair et al. that their antibodies are effective when administered to neutralize TNF-α in vivo.

30. No claims are allowable.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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